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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,303	10/23/2003	Thomas Primiano	02-1133-C	7346

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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/692,303	PRIMIANO ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *1-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-9 are all the pending claims for this application.

2. Claim 8 was amended in the Response of September 14, 2006. Applicants identify written support for the amendment to recite "for the treatment of carcinoma" in [0011, 0048, 0050] of the specification. The amendment has been considered in view of the original specification and entered.

3. Claims 8 and 9 are all the pending claims under examination.

4. Applicants amendments to the claims have necessitated new grounds for rejection. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections Withdrawn

Specification

5. The objection to the Abstract of Disclosure for reciting legal language is withdrawn in view of the amended abstract.

Rejections Maintained

35 USC § 102

6. The rejection of Claims 8 and 9 under 35 U.S.C. 102(b) as being anticipated by Hoefnagel et al. (European J. Nuclear Medicine 28:359-368 (March 2001) is maintained.

Applicant argues that "Hoefnagel et al. do not teach or suggest the use of an anti-L1CAM antibody or L1CAM-binding fragment have any effect on growth of carcinoma cells, and thus do not teach or suggest that LICAM antibodies are useful for the treatment of carcinoma" (p 4, ¶5 of the Response). Applicants have further amended composition Claims 8 and 9 by introducing a non-limiting "use" of the composition "for the treatment of a carcinoma". Applicant's arguments and the amendment have been considered but are not found persuasive.

Specifically, with respect to chemical compositions and properties, a long line of cases stands for the principal that the recitation of a new property of a known compound does not establish patentable novelty over the old compound. (*E.g.*, *In re Crish*, 393 F.3d 1253, 1258, 73 USPQ2d 1364, 1368 (CA FC 2004) ("the PTO's position that the discovery of new properties of a known material does not make claims reciting those properties novel is correct"); *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("The discovery of a new property or use of a previously known composition, even when that property and use are unobvious from prior art, can not impart patentability to claims to the known composition ."); *Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 782, 227 USPQ 773, 778 (Fed. Cir. 1985) (composition claim reciting a newly discovered property of an old alloy did not satisfy section 102 because the alloy itself was not new); *In re Pearson*, 494 F.2d 1399, 1403, 181 USPQ 641, 644 (CCPA 1974) (intended use of an old composition does not render composition claim patentable); *In re Benner*, 174 F.2d 938, 942, 82 USPQ 49, 53 (CCPA 1949) ("no provision has been made in the patent statutes for granting a patent

upon an old product based solely upon discovery of a new use for such product"). Stated another way, a claim to a compound in which the sole "novelty" recited in the claim is a newly discovered property, the claim does not distinguish the claimed subject matter from the known compound for the purposes of anticipation. An example illustrates this point. Where the prior art discloses a specific compound X and that it is useful for treating certain heart conditions, a later claim to the same compound but reciting a new property, e.g., "Compound X that grows hair" is anticipated by the earlier disclosure of compound X, notwithstanding that the new property is newly discovered and unobvious. The reason it is unpatentable is that the substance, compound X, is the same. Only additional information about the old compound has been provided.)

Thus, because the use of the composition is not further limiting for the composition claims over the prior art reference, Hoefnagel et al., the anticipation rejection stands.

7. The rejection of Claims 8 and 9 under 35 U.S.C. 102(b) as being anticipated by Carrel et al. (Nuclear Medicine Biol. 24(6):539-546 (August 1997) is maintained.

Applicant argues that "Carrel et al. do not teach or suggest the use of an anti-LICAM antibody or LICAM-binding fragment can be used to treat carcinoma" (p. 5, ¶3). Applicants have further amended composition Claims 8 and 9 by introducing a non-limiting "use" of the composition "for the treatment of a carcinoma". Applicant's arguments and the amendment have been considered but are not found persuasive.

See the Examiner's comments supra addressing the case law on intended use limitations for composition claims. Accordingly, because the use of the composition is not further limiting for the composition claims over the prior art reference, Carrel et al., the anticipation rejection stands.

8. The rejection of Claims 8 and 9 under 35 U.S.C. 102(b) as being anticipated by Mujoo et al. (J. Biol. Chem. 261:10299-10305 (1986) as evidenced by Wolff et al (J. Biol. Chem. 263:11943-11947 (1988)) is maintained.

Applicant argues "the LICAM antibodies taught by Mujoo et al. were unable to recognize carcinoma cells (see Table II on page 10302). Wolff et al., as pointed out by the Action, merely discloses that the Mujoo et al. antibody can bind human and murine L1 antigens. Neither one of these references teaches or suggests that an anti-L1CAM antibody or L1CAM-binding fragment can be used to treat carcinomas" (p. 5, ¶5). Applicant's arguments and the amendment have been considered but are not found persuasive.

See the Examiner's comments supra addressing the case law on intended use limitations for composition claims. Accordingly, because the use of the composition is not further limiting for the composition claims over the prior art reference, Mujoo et al. as evidenced by Wolff et al., the anticipation rejection stands.

9. The rejection of Claims 8 and 9 under 35 U.S.C. 102(b) as being anticipated by Patel et al. (Hybridoma 10:481-491 (1991)) is maintained.

Applicant argues that "Patel et al. do not teach or suggest the use of an anti-LICAM antibody or LiCAM-binding fragment for the treatment of carcinoma" (p. 6, ¶1). Applicant's arguments and the amendment have been considered but are not found persuasive.

See the Examiner's comments supra addressing the case law on intended use limitations for composition claims. Accordingly, because the use of the composition is not further limiting for the composition claims over the prior art reference, Patel et al., the anticipation rejection stands.

35 USC § 103

10. The rejection of Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rathjen et al. (EMBO J. 3:1-10 (1984)) in view of Cleland et al. (J. Pharm. Sci. 90:310-321 (2001)) is maintained.

Applicant argues that "Rathjen et al. do not teach, suggest, or make obvious to those of skill in the art the use of an anti-LiCAM antibody or LICAM-binding fragment for the treatment of carcinoma. Cleland et al. do not cure this deficiency. Specifically, Cleland et al. merely teach excipients for stabilizing a monoclonal HER2 antibody. Cleland et al. do not teach use of an anti-LICAM antibody or LICAM binding fragment for the treatment of carcinoma" and that "the combination of Rathjen et al. and Cleland et al. do not render the instant claim obvious, because the cited references do not teach or suggest pharmaceutical compositions for the treatment of carcinoma" (p. 6, ¶5).

Applicant's arguments and the amendment have been considered but are not found persuasive.

See the Examiner's comments supra addressing the case law on intended use limitations for composition claims. Accordingly, because the use of the composition is not further limiting for the composition claims over the combined prior art references, Rathjen et al. and Cleland et al., the obviousness rejection stands.

11. The rejection of Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff et al. (J. Biol. Chem. 263:11943-11947 (1988)) in view of Cleland et al. (J. Pharm. Sci. 90:310-321 (2001)) is maintained.

Applicant argues that "Wolff et al. teach "the potential involvement of 5G3 or L1 in various human neurological disorders." Wolff et al. do not teach, suggest, or make obvious to those of skill in the art the use of an anti-L1CAM antibody or L1CAM-binding fragment for the treatment of carcinoma. Cleland et al., as discussed above, does not teach or suggest the use of L1CAM" (p. 7, ¶1). Applicant's arguments and the amendment have been considered but are not found persuasive.

See the Examiner's comments supra addressing the case law on intended use limitations for composition claims. Accordingly, because the use of the composition is not further limiting for the composition claims over the combined prior art references, Wolff et al. and Cleland et al., the obviousness rejection stands.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the commercial L1CAM antibodies, UJ127 and 5G3, to inhibit cell proliferation of tumor cell that expresses L1CAM, in particular tumor cells from breast cancer, colon cancer, cervical cancer, melanoma, neuroblastoma, small cell lung cancer, lymphoma, does not reasonably provide enablement for making any L1CAM antibody and using the L1CAM antibody to inhibit proliferation of just any carcinoma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Claims 8 and 9 are drawn to a composition comprising any L1CAM antibody or L1CAM-binding fragment thereof and a pharmaceutically-acceptable excipient for the treatment of any carcinoma.

A) The composition of Claims 8 and 9 is not enabled for treating any carcinoma with just any L1CAM antibody or L1CAM binding fragment thereof.

Claims 8 and 9 are drawn to the pharmaceutical composition having an intended use "for the treatment of carcinoma." The claims encompass treating just any carcinoma with any L1CAM antibody or L1CAM binding fragment thereof.

The specification teaches in general methods for inducing cell death in tumor cells, most preferably human tumor cells in any tumor cell that expresses L1CAM, particular tumor cells from breast cancer, colon cancer, cervical cancer, melanoma, neuroblastoma, small cell lung cancer, lymphoma and other tumor cell types where the inventive methods are practiced using the pharmaceutical compositions [0048]. The only L1CAM antibodies disclosed in the pharmaceutical composition for treating a carcinoma are the commercially available anti-L1CAM monoclonal antibodies, UJ127 (IgG1, NeoMarkers (Fremont, Calif.) and 5G3 (IgG2a; BD PharMingen, San Diego) (Example 1) [0050]. Both antibodies were shown to induce a 3-6 fold decrease in the cell number of all four tumor cell lines (i.e., cMDA-MB231 and MCF-7 breast carcinoma cell lines, HeLa cervical carcinoma and HCT116 colon carcinoma lines) relative to their corresponding isotype controls. A rabbit polyclonal anti-L1CAM antiserum, which was obtained from Dr. H. Asou (Keio University, Tokyo, Japan) showed a cytotoxic effect at

1:50 dilution [0053]. The anti-L1CAM monoclonal antibodies showed the appearance of micronucleated or apoptotic cells, indicative of the induction of cell death (FIG. 1C).

The treatment of carcinomas with L1CAM antibodies is art recognized by, for example, MCF7 breast carcinoma using UJ127 and 5G3 (Primiano et al. Cancer Cell 4:41-53 (July 2003)). Arlt et al. (Cancer Research 66(2):936-943 (2006), in particular, see Table 1) demonstrated a differential effect of three different L1CAM Mabs (L1-11A, chCE7, HEA125) on proliferation of different human tumor cell lines (SKOV3- ovarian carcinoma; Fohn renal cell carcinoma; Caki-2 renal carcinoma; SK-N-BE2c neuroblastoma; SK-N-As neuroblastoma; HCT116 colon carcinoma). These results are dispositive to there being enablement for the claim scope encompassing any cancers being treatable with any anti-L1CAM antibody. Accordingly, the claims are enabled for only those L1CAM antibodies supported by the specification and known in the art to inhibit carcinoma cell proliferation. One skilled in the art would be required to perform undue experimentation in practicing the claimed intended use because they would be required to identify an infinite scope of L1CAM antibodies in a pharmaceutical composition having the intended use of treating any cancer.

B) Drug delivery of high molecular weight molecules to cancers is unpredictable

The composition comprising an L1CAM antibody or L1CAM-binding fragment thereof of claims 8 and 9 would have an approximate molecular weight of 250 kD. The difficulty in accomplishing uptake of large therapeutic molecules into some tumors is well established in cancer therapeutics. Jain discloses the art known barriers to the

delivery of drugs into solid tumors (Scientific American July 1994 pp. 58-65). Impediments to drug delivery include (1) nonuniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) high liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2).

Chatterjee et al state the art recognized experience that for any novel therapy, the transition for the laboratory to the clinic (animal experiments to the bedside) is a quantum leap (Cancer Immunol. Immunother. 38:75-82 (1994); see Introduction). Results obtained under controlled conditions and in inbred animals, often differ from the clinical response obtained in patients. This applies to strategies drawn to cancer therapy. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

The specification does not disclose whether the composition is effective in animals with a pre-existing cancer, and this is a significant omission in view of the well-known immunosuppressive effects of certain tumors. The criticality of a working example encompassing all of the intended use steps, especially the treatment of a pre-existing carcinoma with any L1CAM antibody or binding fragment thereof, is underscored by Gura et al (Science 278:1041-1042 1997)) in a discussion of potential shortcomings of extrapolating from in vitro studies and animal studies to similar procedures in cancer patients. Gura et al teaches that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, second col, second full paragraph) and that there were "gross difference in sensitivity in real tumors in mice and in the clonogenic assay" (page 1042, second col, second full paragraph). Further, Gura teaches that clonogenic assays "cannot tell researchers how anticancer drugs will act in the body" (page 1042, first-second col, bridging paragraph). One skilled in the art would reasonably conclude that evidence obtained in mouse xenograft models would not necessarily correlate with results expected in humans patients much less experiments limited to only a few cell lines as in the instant case.

It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teachings of the specification alone and the specification fails to enable the specific, site-directed accumulation of the anti-L1CAM antibody or binding-fragment thereof to just any carcinoma or carcinoma cell with the intention of treating the carcinoma or carcinoma cell.

c) Conclusion

The skilled artisan at the time the invention was made recognized the lack of predictability of the nature of the art and state of the prior art to which the instant invention pertains. Also, such disclosures clearly indicate that the amount of direction or guidance presented in the specification is limited, and would not permit a person skilled in the art to use the invention without undue experimentation at the time the invention was made. In view of the undue experimentation that would be required to make and use just any anti-L1CAM antibody or binding fragment thereof for treating just any carcinoma or carcinoma cell with a reasonable expectation of success, absent a specific and detailed description in Applicant's specification of how to effectively make and use the claimed composition and absent working examples providing evidence which is reasonably predictive that the claimed composition is effective in treating any carcinoma or carcinoma cell, commensurate in scope with the claimed invention.

Conclusion

13. No claims are allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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